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Original research

Impact of whole breast irradiation, endocrine therapy or their combination on outcomes of early-stage, luminal A-like, low-risk, breast cancer patients aged 65 years or over: Insights from the EUSOMA database

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ABSTRACT

Aim: To assess oncological outcomes in early-stage, luminal A-like, low-risk, breast cancer patients aged 65 years or more after conserving surgery followed by endocrine therapy (ET) and/or whole breast irradiation (WBI) or no adjuvant therapy.

Methods: Data from patients treated in EUSOMA-certified breast units between 2010 and 2022 were collected. Univariable and multivariable analyses for local, nodal, distant recurrences, breast cancer specific survival (BCSS), and overall mortality were conducted. Potential treatment-related determinants included adjuvant ET alone, WBI alone, ET+WBI or no adjuvant therapy.

Results: Breast cancer patients (9660) from 72 Breast Units across 14 European countries were enrolled. Tumours were pT1 in 85.8 % of cases. All tumours were luminal A-like. All patients had negative nodes. Adjuvant ET alone was prescribed for 806 (8.3 %) and WBI alone was delivered to 386 (4.0 %); ET and WBI were combined (ET+WBI) in 8154 (84.4 %) patients. No adjuvant therapy was given to 314 patients (3.3 %). The median follow-up was 1.87 years (first quartile 0.81, third quartile 4.16), and the mean was 2.62 years (range 0.003–13.82 years). Compared with no adjuvant therapy, multivariable analysis showed ET+WBI significantly improved in-breast tumour recurrence-free survival (IBTRFS) (HR 0.28, CI 95 % 0.10 −0.79; $p = 0.016$) and BCSS (HR 0.12; CI 95 %: 0.03 −0.51; $p = 0.004$). ET alone (HR 0.57; CI 95 %: 0.35 −0.90; $p = 0.017$), WBI alone (HR 0.51; CI 95 %: 0.27 −0.95; $p = 0.033$) and both treatments combined (HR 0.26; CI 95 %: 0.16 −0.42; $p < 0.001$) significantly lowered mortality.

Conclusions: Despite a short follow-up, results from this large series of low-risk breast cancer patients who had undergone conserving surgery, showed adjuvant treatments impacted positively upon outcomes.

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1. Introduction

In patients who receive breast conserving surgery (BCS), whole breast irradiation (WBI) is the standard of care, as it significantly reduces the risk of relapse and mortality [1–3]. However, the risk *vs* benefit analysis of WBI identified many factors advocating against it: older age, short life expectancy, risk of toxicity, comorbidities, disabilities, frailty, poor general health, poor psychological and cognitive status. Furthermore, the benefits of post-operative WBI vary with tumour subgroup and WBI may even become over-treatment in older patients with low-risk tumours who are thus exposed to the risk of toxicity. On the other hand, a prospective cohort study has recently documented significant geographical variation in the use of radiation therapy (RT) with no influence of geriatric domains on decision-making [4].

Several phase III randomized studies, that included overall more than 7000 patients, were designed to determine whether WBI could be omitted in well-selected low-risk patients [5–15]. Ages varied; in a few studies patients were over 65 −70 years [5,7,14], while others adopted 60 years or under as cut-offs [6,9,10–13]. All tumours were T1 or T2; most were hormone receptor positive, but the HER2 status was unknown for the majority. Lymph nodes were negative in all but one study [11]. After BCS, most patients received endocrine therapy (ET). One report stated that adjuvant systemic therapy had been administered according to axillary nodal status (14 % of patients had positive axillary nodes) and biological tumor parameters. Consequently, although not reported, some patients might have undergone chemotherapy [11]. Results from all studies indicated that WBI reduced the risk of in-breast tumor relapse (IBTR), thus improving local relapse-free survival (LRFS). It did not, however, impact upon overall survival (OS) or, when reported, on distant recurrence free survival (DRFS) and/or breast cancer specific survival (BCSS). The trials were analyzed in depth in a review article which we refer the reader to [16]. In 2023 46 % of Saint Gallen panelists voted against routine use of RT, because of the lack of OS benefit, and 35 % in favor, because it lowered IBTRs [17].

To assess whether whole-breast irradiation (WBI) could be safely omitted after BCS, the present study evaluated oncological outcomes in patients aged 65 years old or over (just as in the PRIME II trial [14,15]), with early-stage, low-risk, luminal A-like breast cancer, comparing those who received post-operative WBI with those who did not. Patient data were sourced from the EUSOMA database (EusomaDB), a prospectively maintained dataset of breast cancer cases initiated in 2006, which currently includes information on over 200,000 patients. As detailed elsewhere [3], the database comprises 166 variables covering patient and tumor characteristics, treatment details and follow-up. No personal identifiers are included at any point in the database. Present study design is supported by the fact that nowadays more and more relevance is given to large-scale observational data, like the EusomaDB, as a complement to the results of randomized controlled trials. There is evidence for an increasing role of data which derives from routine clinical practice, as it provides additional insights into the relation between treatments and outcome [18]. The comparison between RCTs and EusomaDB evidence forms the basis of our discussion.

2. Patients and methods

Patient data were sourced in the EusomaDB. Inclusion criteria were age $\geq$65 years, newly diagnosed pT1–2, pN0, luminal A-like breast cancer, treated with BCS. Exclusion criteria were age $<$ 65 years, T3–4, N+, no luminal A-like breast cancer, mastectomy. Patients were accrued from 72 breast units in 14 European countries (Austria=3, Belgium=9, Croatia=1, Cyprus=1, France=1, Germany=15, Greece=1; Italy=28, Poland=1, Portugal=3, Spain=1, Sweden=1, Switzerland=5, The Netherlands=2). All breast cancer centres had undergone or were undergoing voluntary EUSOMA certification between 2010 and 2022 [19,20]. Because the data used in this study were extracted from the de-identified EusomaDB files, research was exempt from institutional review board approval. Since the data are anonymous GDPR rules do not apply. No other action or authorization is required from the participating Breast Centres.

2.1. Endpoints

The primary end-point was IBTR, defined as histologically confirmed tumour reappearance in the same breast as the primary tumour.

Secondary end-points were regional relapse (RR), distant metastases (DM), BCSS and OS. RR was defined as disease occurrence in the ipsilateral regional lymph nodes; DM as metastases in distant organs; BCSS as the time between the start of treatment and death due to breast cancer; OS as the time between the start of treatment and death from any cause.

Results from each endpoint derived from the cancer registry and/or from follow-up information provided by each participating centre which was inserted into the EusomaDB.

2.2. Statistical analysis

Univariable and multivariable Cox analyses assessed the risk for IBTR, RR, DM, breast cancer specific death and overall death. The potential determinants included age, tumour size, grade and therapy (comparing four groups: no adjuvant therapy, ET alone, WBI alone, ET and WBI). All covariates were included in the uni- and multi- variable models. Variables for the multivariable models were selected by means of a stepwise procedure that was applied separately to each outcome. This procedure confirmed the inclusion of all four variables for all endpoints. A saturated model with all four variables for each endpoint was adopted for several reasons: 1) to ensure uniformity and consistency, 2) avoid differences in model specification, as driven solely by automated selection criteria and 3) compare estimated effects directly across endpoints.

5-year survivals were estimated with the Kaplan-Meier method, and survival curves were compared using the log-rank test.

All statistical analyses were performed using R version 4.3.2 (© The R Foundation); statistical significance was set at $p < 0.05$.

3. Results

Between January 2010 and December 2022, 9660 patients (median age 73 years; range 65 −100) were identified. Patient accrual increased from 69 in 2010 to around 1400 annually in the 2018–2022 period.

All patients had received BCS. Axillary status had been evaluated by means of sentinel node biopsy alone in 9068 (93.9 %) patients, axillary lymph node dissection alone in 79 (0.8 %), both procedures in 222 (2.3 %). In 249 cases (2.6 %) no axillary surgery had been performed and in 42 (0.4 %) no information on axillary surgery was available. Median tumour size was 12 mm (range 1–50 mm). pT1 accounted for 8290/9660 lesions (85.8 %) and pT2 for 1370 (14.2 %). pT2 tumours were up to 3 cm in size in 1157/1370 (84.4 %) and $>$ 3 cm in 213 (15.5 %). Grade 1 tumours were found in 2573/9660 (26.6 %), grade 2 in 6217 (64.4 %) and grade 3 in 870 (9.0 %). All tumours were Luminal A-like. Median Ki67 was 10 % (range 0 %-20 %). All patients had negative nodes.

WBI was administered to 8540/9660 patients (88.4 %); it was given alone to 386 (4.0 %) and in association with adjuvant ET to 8154 patients (84.4 %). ET alone was prescribed for 806 patients (8.3 %). Neither WBI nor ET was given to 314 patients (3.3 %). All data and their distribution are shown in Table 1. Fig. 1 shows postoperative treatment distribution.

The median follow-up was 1.87 years (first quartile 0.81, third quartile 4.16), and the mean was 2.62 years (range 0.003–13.82 years).

Data on IBTR were available for 7664/9660 patients (79 %). IBTR occurred in 59 patients (0.8 %). The 5-year probability of IBTR-free survival (IBTRFS) was 79.9 % in patients who did not receive any

adjuvant therapy, 96.3 % in those who received only ET, 96.7 % after WBI alone and 99 % when both treatments were combined (Table 2 and Fig. 2, Panel A). Compared with no therapy, univariable analysis showed WBI, ET whether alone or together significantly improved IBTRFS ($p = 0.015$; $p = 0.01$; $p < 0.001$, respectively,). Multivariable analysis demonstrated that only WBI in association with ET significantly improved IBTRFS (HR 0.28, CI 95 % 0.10–0.79; $p = 0.016$) (Table 2).

In univariable analysis, IBTRFS was significantly worse in pT2 tumours up to 3 cm in size than in pT1 tumours ($p = 0.004$) and in grade 3 tumours than in grade 1 lesions ($p = 0.003$). Multivariable analysis confirmed that only grade 3 tumours were a risk factor for significantly worse IBTRFS (HR 2.99, CI 95 % 1.30–6.87; $p = 0.010$) (Table 2).

Data on RR were available for 7342/9660 patients (76 %). RR occurred in 25 patients (0.34 %). The 5-year probability of RR-free survival (RRFS) was almost 100 % in all subgroups (Table 2 and Fig. 2, Panel B). Compared with ET alone, univariable and multivariable analyses showed neither WBI nor WBI plus ET significantly impacted on RRFS (Table 2).

Compared with pT1 tumours, pT2 tumours up to 3 cm in size significantly worsened RRFS in both univariable ($p = 0.004$) and multivariable analyses (HR 2.94, CI 95 % 1.16–7.45; $p = 0.023$) (Table 2).

Data on DM were available for 7744/9660 patients (80 %). DM occurred in 88 patients (1.1 %); they were preceded by nodal relapse in 9 patients. The 5-year probability of DM-free survival (DMFS) ranged from 89.0 % without any adjuvant therapy to 98.4 % with both WBI and ET (Table 2 and Fig. 2, Panel C). Univariable and multivariable analyses did not show any impact of WBI, ET and WBI+ET on DMFS compared with no therapy (Table 2).

pT2 tumours had significantly worse DMFS in univariable ($p < 0.001$ for tumours up to and over 3 cm in size) and multivariable analyses (tumours up to 3 cm: HR 3.73, CI 95 % 2.29–6.09; $p < 0.001$; tumours over 3 cm: HR 5.31, CI 95 % 2.21–12.75; $p < 0.001$). Grade 3 tumours had significantly worse DMFS in univariable ($p < 0.001$) and multivariable (HR 2.93, CI 95 % 1.43–5.98; $p = 0.003$) analyses (Table 2).

Table 1
Therapies and tumour characteristics.

	N° patients	%
Breast Surgery		
BCS	9.660	100 %
Axillary Surgery		
SLNB	9.068	93.9 %
ALND	79	0.8 %
SLNB+ALND	222	2.3 %
No Surgery	249	2.6 %
NA	42	0.4 %
Tumor Stage		
pT1	8.290	85.8 %
pT2	1.370	14.2 %
≤ 3 cm	1.157	
> 3 cm	213	
Grading		
G1	2.573	26.6 %
G2	6.217	64.4 %
G3	870	9.0 %
Nodal Stage		
pN0	9.660	100 %
Post operative treatment		
ET	8.960	92.8 %
WBI	8.540	88.4 %
WBI + ET	8.154	84.4 %
ET alone	806	8.3 %
WBI alone	386	4.0 %
No adjuvant therapy	314	3.3 %

Legend:
BCS = breast conserving surgery, SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection, ET = endocrine therapy, WBI = whole breast irradiation, NA = not available

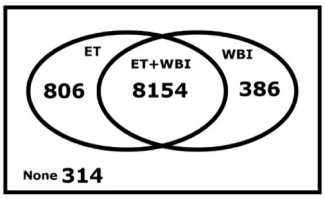

Fig. 1. Postoperative treatment distribution.

Data on BCSS were available for 8504/9660 patients (88 %). Breast cancer-related deaths occurred in 27 patients (0.3 %). The 5-year probability of BCSS ranged from 97.0 % with only WBI to 99.6 % with WBI+ET (Table 2 and Fig. 2, Panel D). Compared with no therapy, univariable ($p < 0.001$) and multivariable (HR 0.12, CI 95 % 0.03–0.51; $p = 0.004$) analyses showed that only ET+WBI significantly improved BCSS (Table 2).

pT2 tumours over 3 cm in size had significantly worse BCSS in univariable ($p < 0.001$) and multivariable analyses (HR 5.98, CI 95 % 1.57–22.83; $p = 0.009$) (Table 2).

Data on mortality were available for 8614/9660 patients (89 %), showing 314 (3.6 %) patients had died. The 5-year probability of OS was 65.6 % after no therapy, which increased to 83.5 % with ET alone, 86.3 % with WBI alone and 94.7 % with WBI+ET (Table 2 and Fig. 2, Panel E). Compared with no therapy, WBI, ET and both together were associated with significantly lower mortality in univariable ($p < 0.001$ for all treatments) and multivariable analyses (WBI alone: HR 0.51, CI 95 % 0.27–0.95; $p = 0.033$; ET alone: HR 0.57, CI 95 % 0.35–0.90; $p = 0.017$; WBI and ET: HR 0.26, CI 95 % 0.16–0.42; $p < 0.001$) (Table 2).

Univariable analysis showed OS was significantly worse for pT2 tumours up to and over 3 cm in size ($p < 0.001$ for both) and grade 3 ($p = 0.033$) tumours. Multivariable analyses confirmed only pT2 tumours > 3 cm in size as a risk factor for worse OS (HR 3.18; CI 95 % 1.97–5.15; $p < 0.001$) (Table 2).

Age emerged as a significant risk factor for IBTRFS, BCSS and OS in univariable ($p < 0.001$ for all outcomes) and multivariable analysis (LRFS: HR 1.11, CI 95 % 1.06–1.17; $p = < 0.001$; BCSS: HR 1.10, CI 95 % 1.03–1.17; $p = 0.006$; OS: HR 1.11, CI 95 % 1.09–1.13; $p < 0.001$) (Table 2).

4. Discussion

In this large database-derived series of low-risk breast cancer patients who had undergone BCS, adjuvant WBI + ET significantly improved IBTRFS. WBI is known to protect against local relapse, thus improving IBTRFS, even in patients with low-risk disease. In these patients, nine randomized clinical trials all showed that WBI significantly reduced the risk of local relapse. Their designs were, however, different. One compared tamoxifen (TAM) alone *vs* RT + placebo *vs* RT+TAM [5]. Others compared TAM alone *vs* RT + TAM [6,7]. The others compared RT *vs* no RT, administering adjuvant systemic therapy (mainly ET) on the basis of risk factors and local, national or international guidelines [9–11,13,14]. Finally, the British Association of Surgical Oncology (BASO) II trial [12] (which had a 2 × 2 factorial design to compare outcomes after no adjuvant therapy, WBI or TAM or both) showed a higher IBTR rate in patients who received no adjuvant therapy. IBTR was reduced similarly by both RT and TAM alone, and to a greater extent, by both treatments together. Like the four arms of the BASO II trial [12] and of a series from the Memorial Sloan Kettering Cancer Center [21], the present study analyzed four groups (no therapy, WBI, ET, WBI+ET), finding that IBTRFS was worst in patients who did not receive adjuvant therapy. Compared with no therapy, all therapeutic approaches were associated with improved IBTRFS in univariable analysis, but only the combination of ET+WBI remained significant in multivariable analysis.

Table 2.

					Univariable			Multivariable *		
		Cases	N° of Events	%	HR	IC 95 %	p-value	HR	IC 95 %	p-value
In breast recurrence free survival.										
		7664	59	0,8						
Therapy	**No adjuvant**	183	7	3,8	ref.			ref.		
	ET alone	641	11	1,7	0,29	0,11–0,75	**0,01**	0,56	0,20–1,58	0,271
	WBI alone	303	2	0,7	0,14	0,03–0,68	**0,015**	0,26	0,05–1,38	0,114
	WBI+ET	6537	39	0,6	0,08	0,04–0,18	**< 0,001**	0,28	0,10–0,79	**0,016**
Size	**0–20 mm**	6610	46	0,7	ref.			ref.		
	21–30 mm	895	13	1,5	2,51	1,35–4,65	**0,004**	1,56	0,80–3,03	0,192
	31 + mm	159	0	0	0		0,994	0		0,997
Grade	**I**	2138	10	0,5	ref.			ref.		
	II	4827	35	0,7	1,5	0,74–3,03	0,259	1,22	0,60–2,51	0,586
	III	699	14	2	3,52	1,56–7,95	**0,003**	2,99	1,30–6,87	**0,010**
Age	**Median**	73,51	77,9		1,15	1,11–1,19	**< 0,001**	1,11	1,06–1,17	**< 0,001**
Regional recurrence free survival.										
		7342	25	0,3						
Therapy	**ET alone**	585	4	0,7	ref.			ref.		
	WBI alone	300	1	0,3	0,66	0,07–5,91	0,708	0,65	0,07–5,93	0,701
	WBI+ET	6308	20	0,3	0,44	0,15–1,28	0,13	0,49	0,16–1,55	0,226
	No adjuvant	149	0	0	0	0,00-Inf	0,996	0	0,00-Inf	0,998
Size	**0–20 mm**	6364	17	0,3	ref.			ref.		
	21–30 mm	839	7	0,8	3,6	1,49–8,70	**0,004**	2,94	1,16–7,45	**0,023**
	31 + mm	139	1	0,7	3,79	0,50–28,73	0,198	2,67	0,34–21,08	0,351
Grade	**I**	2077	5	0,2	ref.			ref.		
	II	4597	15	0,3	1,3	0,47–3,58	0,611	1,15	0,41–3,22	0,786
	III	668	5	0,7	2,7	0,78–9,35	0,116	2,07	0,57–7,50	0,269
Age	**Average**	73,47	74,72		1,06	1,00–1,13	0,064	1,03	0,96–1,11	0,417
Metastasis free survival.										
		7744	88	1,1						
Therapy	**No adjuvant**	177	4	2,3	ref.			ref.		
	ET alone	651	11	1,7	0,56	0,18–1,76	0,32	0,66	0,20–2,15	0,485
	WBI alone	307	7	2,3	0,92	0,27–3,15	0,895	1,19	0,32–4,41	0,790
	WBI+ET	6609	66	1	0,29	0,11–0,81	**0,018**	0,35	0,11–1,07	0,065
Size	**0–20 mm**	6675	54	0,8	ref.			ref.		
	21–30 mm	905	28	3,1	4,36	2,76–6,89	**< 0,001**	3,73	2,29–6,09	**< 0,001**
	31 + mm	164	6	3,7	5,91	2,53–13,79	**< 0,001**	5,31	2,21–12,75	**< 0,001**
Grade	**I**	2128	13	0,6	ref.			ref.		
	II	4903	53	1,1	1,76	0,96–3,22	0,069	1,52	0,82–2,81	0,183
	III	713	22	3,1	4,43	2,23–8,81	**< 0,001**	2,93	1,43–5,98	**0,003**
Age	**Average**	73,49	74,45		1,04	1,01–1,08	**0,013**	1	0,96–1,03	0,859
Breast cancer specific survival.										
		8504	27	0,3						
Therapy	**No adjuvant**	181	3	1,7	ref.			ref.		
	ET alone	678	4	0,6	0,25	0,06–1,12	0,07	0,23	0,05–1,10	0,065
	WBI alone	318	4	1,3	0,57	0,13–2,56	0,461	0,66	0,14–3,23	0,610
	WBI+ET	7327	16	0,2	0,08	0,02–0,26	**< 0,001**	0,12	0,03–0,51	**0,004**
Size	**0–20 mm**	7341	17	0,2	ref.			ref.		
	21–30 mm	985	7	0,7	3,45	1,42–8,40	**0,006**	2,31	0,91–5,88	0,078
	31 + mm	178	3	1,7	9,95	2,88–34,44	**< 0,001**	5,98	1,57–22,83	**0,009**
Grade	**I**	2298	2	0,1	ref.			ref.		
	II	5459	18	0,3	3,82	0,89–16,48	0,072	3,49	0,80–15,31	0,097
	III	747	7	0,9	7,76	1,57–38,33	**0,012**	4,50	0,86–23,54	0,075
Age	**Average**	73,32	78,63		1,18	1,12–1,24	**< 0,001**	1,10	1,03–1,17	**0,006**
Overall mortality.										
		8614	314	3,6						
Therapy	**No adjuvant**	196	31	15,8	ref.			ref.		
	ET alone	703	62	8,8	0,41	0,27–0,63	**< 0,001**	0,57	0,35–0,90	**0,017**
	WBI alone	323	18	5,6	0,32	0,18–0,58	**< 0,001**	0,51	0,27–0,95	**0,033**
	WBI+ET	7392	203	2,7	0,11	0,08–0,16	**< 0,001**	0,26	0,16–0,42	**< 0,001**
Size	**0–20 mm**	7421	238	3,2	ref.			ref.		
	21–30 mm	1006	57	5,7	1,94	1,45–2,59	**< 0,001**	1,21	0,89–1,65	0,227
	31 + mm	187	19	10,2	4,31	2,69–6,88	**< 0,001**	3,18	1,97–5,15	**< 0,001**
Grade	**I**	2318	72	3,1	ref.			ref.		
	II	5528	197	3,6	1,14	0,87–1,50	0,329	1,05	0,79–1,38	0,746
	III	768	45	5,9	1,5	1,03–2,19	**0,033**	1,23	0,84–1,80	0,296
Age	**Average**	73,41	78,34		1,15	1,13–1,17	**< 0,001**	1,11	1,09–1,13	**< 0,001**

* Multivariable models all adjusted also per calendar year

Legend:

ET = endocrine therapy, WBI = whole breast irradiation, HR = hazard ratio

Little information is available on the impact of tumour size on IBTRFS in these low-risk patients. Only a few patients with T2 tumours were enrolled in six of the nine above-mentioned randomized trials [6, 9–11,13,14] and tumor size was up to 3 cm in three of six [10,11,14]. According to one report [6] as well as the results of a prospective, non-randomized series of patients who received only TAM [22], T2

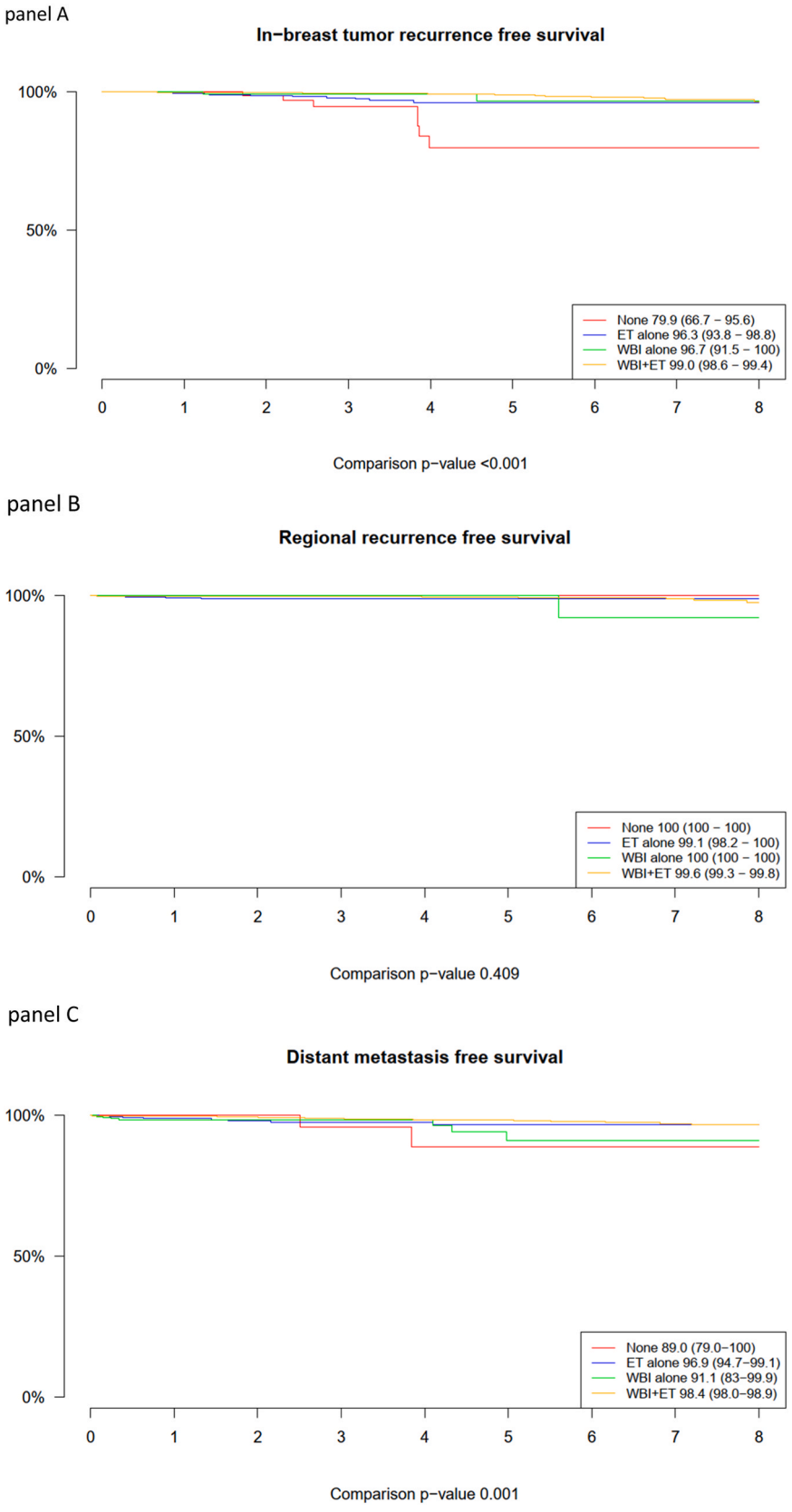

Fig. 2. 5-year survival probabilities.

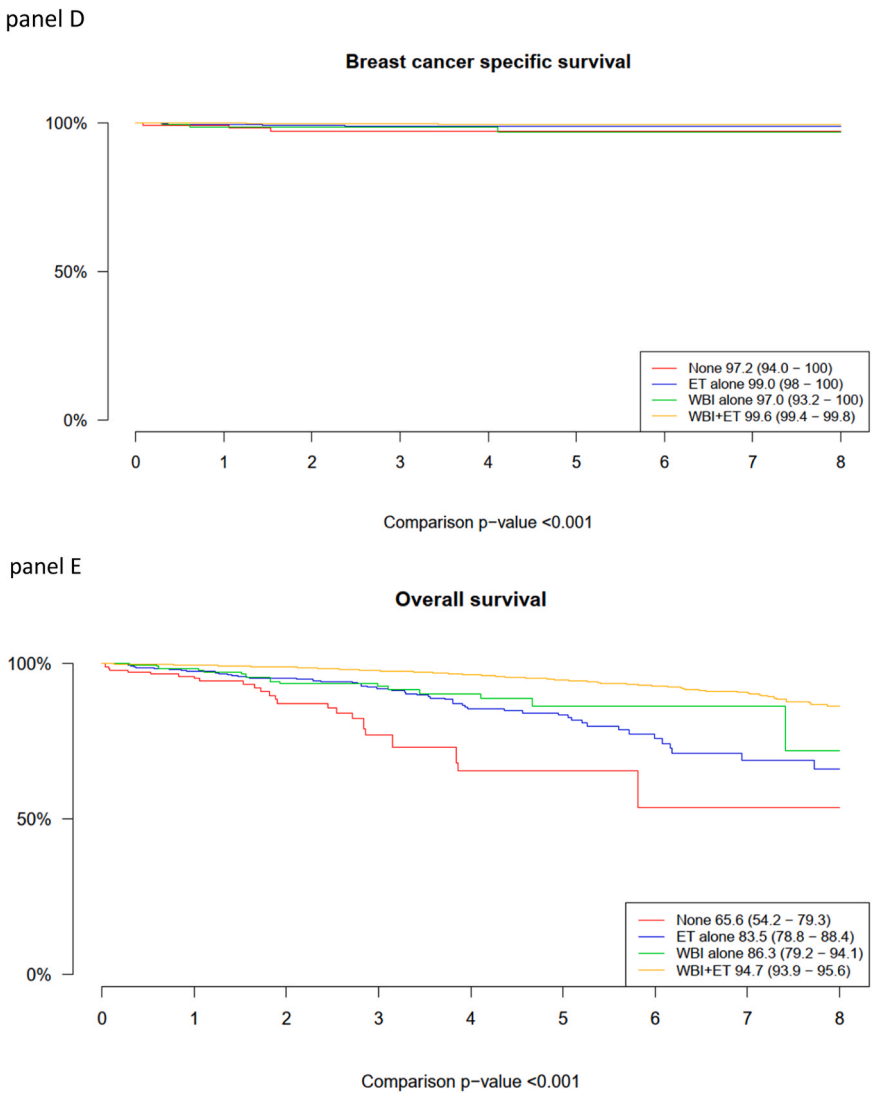

Fig. 2. (*continued*).

tumours were associated with a higher IBTR rate, suggesting that patients with T2 disease should receive RT in order to lower the IBTR rate. In the present study, pT2 tumours up to 3 cm impacted on IBTRFS only in univariable analysis, losing significance in the multivariable. No relationship emerged between pT2 tumours >3 cm and IBTRFS, perhaps due to the small sample size. The current multivariable analysis showed that tumour grade 3 was a risk factor for worse IBTRFS. In this regard, no information can be obtained from the nine trials cited above. Indeed, in one of these studies grading did not emerge as a significant risk factor for IBTR [6] and in the Prime II series only 5 % of patients had grade 3 tumours, thus making assessment of their impact impossible [14,15].

Age as analyzed as a continuous variable in the present study, rather surprisingly emerged as a risk factor for poor IBTRFS (HR 1.11) even though it has usually been associated with a lower risk of IBTR [6,23,24]. In attempting to understand this finding we point out that in the present series median age was 73 years (range 65–100) and therefore the effect of age as prognostic factor may have been less significant than in analyses that enrolled patients with wider age ranges. Furthermore, one might speculate that some patients were less likely to receive adjuvant WBI and/or ET because of advanced age and/or associated comorbidities. Admittedly omission of adjuvant treatments in a minority could have been responsible for older age emerging as a risk factor for worse IBTRFS. We were, however, unable to identify if and why WBI and/or ET had been omitted.

In our series, neither adjuvant therapy nor its omission was associated with RRFS, probably because patients were at a very low risk of regional relapse. On the other hand, two of nine randomized trials [6,13] observed that RT administration after BCS significantly lowered RR rates. However, in one of these studies [6] nodal status was assessed clinically in almost 15 % of patients, without specifying whether they had undergone ultrasound scanning which today is the standard of care for an accurate assessment of nodal status. Lack of accurate staging might have contributed to higher RR rates. Tumour size is a known risk factor for RR [23]. In the present analysis, only tumour size up to 3 cm was significantly related to RRFS; as stated above there were too few patients with tumours >3 cm in size to assess their impact on RRFS.

As approximately 97 % of patients received post-BCS therapy, and very few developed DM, we were unable to assess the impact of post-surgical therapies on DMFS. As reported in other series [25,26] pT2 and grade 3 tumours emerged as risk factors for DMFS.

Other findings from the present series were interesting. Compared with no therapy, adjuvant WBI + ET significantly improved BCSS, while WBI, ET and both together were associated with less mortality. None of the phase III studies which randomized older patients to receive WBI or not after BCS showed WBI impacted upon mortality or, when reported, on BCSS. We may hypothesize that none of the single randomized studies that evaluated whether post-operative WBI could be omitted in

early, low-risk patients, had the power to demonstrate that WBI improved these outcomes. Our results do concur, however, with those from the US National Cancer Data Base (NCDB) in 130,194 older, early stage, ER positive breast cancer patients [27]. On the other hand, one might object that selection bias of elderly patients with low-risk cancers might have impacted on this mortality outcome as increased overall mortality in patients without adjuvant treatment could well be related to their age and comorbidities, rather than the lack of adjuvant treatment itself. Poorer survival might not have been unexpected as, when compared with a younger population, older patients, particularly if frail, are more likely to die from other causes than cancer. Indeed, in the present series, 27 patients died of breast cancer compared with 314 who died from unrelated reasons.

Despite its large cohort of almost 10,000 cases, the present study suffers from some limitations. First of all, although missing variables are common in large databases [3], missing data for current outcomes of interest could well constitute a limitation. Secondly, potential flaws might lie in the retrospective nature of the study and the numerical imbalance of 8154 (84 %) patients receiving WBI +ET versus the other 3 groups (ET alone = 806 patients, WBI alone = 386 patients, no therapy = 314 patients). However, the number of patients in each of the other 3 groups was still high enough to provide reliable results as they are in line with sample sizes in most available relevant randomized studies. Finally, the Eusoma large database does not collect data on performance status and comorbidities. As a geriatric population was the focus of the present study, lack of this information could constitute another limitation.

The short follow-up was not a limitation *per se* as our results, on the whole, concurred with others over the same time-frame [12,14]. As events were few in the present analyses, the statistical power was low and should probably be interpreted with caution. Obviously, with a longer follow-up and ET interruption, the impact of risk factors may change over time and more events will be observed, thus lowering the event-free results, bearing in mind that the average life expectancy for a 73-year-old woman in the EU is 15 years [28].

In conclusion, given the good 5-year outcome probabilities, regardless of the adjuvant treatment, the need for both WBI and ET in low-risk patients can reasonably be questioned [12,29,30]. This raises the important question of which treatment should be prioritized. Several studies have shown that ET is frequently interrupted or discontinued due to adverse side effects, which significantly increases the risk of IBTR [15,31,32]. The latest ESMO guidelines [33] consider the omission of RT to be investigational. They state that patients may omit RT, provided they are willing to undergo ET for at least five years and accept its potential side effects, including an increased risk of IBTR. However, modern RT techniques have markedly improved in recent years, enabling more precise targeting of treatment volumes and thereby reducing the risk of adverse events. Moreover, the introduction of ultra-hypofractionated schedules allows WBI to be delivered in as little as one week. Consequently, a modern short course of RT emerges as more attractive and reliable than 5 years ET alone with its adverse side effects or even RT and ET. Supporting these reflections, a preplanned interim analysis from a randomized trial comparing post-BCS RT and ET in patients aged 70 years or more showed that quality of life was significantly better among patients who received RT [34]. Since further data on disease control outcomes and full patient accrual were needed before definitive conclusions could be drawn [34], in 2025 the Saint Gallen panelists strongly recommended both ET and RT for patients similar to those in the present series [35]. Studies incorporating genomic assays and/or biomarkers [36–40] will be help in decision-making as to whether to prioritize RT over ET in this subset of low-risk breast cancer patients.

Study/ethical approval

Data extracted from EUSOMA DB for statistical analysis, being anonymous data, are non-subjects to GDPR rules and no other action or authorization is required from the Breast Centers that undergo the Eusoma Certification procedure.

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CRediT authorship contribution statement

Niccolò M.L. Battisti: Writing – review & editing. **Kwok Leung Cheung:** Writing – review & editing. **Antonio Ponti:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Lorenza Marotti:** Writing – review & editing, Data curation. **Aristei Cynthia:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Giuseppe Curigliano:** Writing – review & editing. **Mariano Tomatis:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Elzbieta Senkus:** Writing – review & editing. **Peter van Dam:** Writing – review & editing. **Donatella Santini:** Writing – review & editing. **Francesco Sardanelli:** Writing – review & editing. **Olaf J. Hartmann:** Writing – review & editing. **Isabel T. Rubio:** Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NB: Advisory board: Pfizer, Abbott, Sanofi, Astellas, Merck, AstraZeneca. Travel grants: Exact Sciences, Pfizer, Lilly, Novartis. Speaker fees: Pfizer, AbbVie, Roche, Sanofi, Novartis, Servier, Gilead, AstraZeneca, Lilly, Exact Sciences, Johnson & Johnson

GC: conflicts of interest are not related to this paper

LF: Advisory Board: MSD, Astra Zeneca

All remaining authors have declared no conflicts of interest

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